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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,530	02/05/2004	George N. Cox III	4152-1-PUS-9	7322

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EXAMINER

LUCAS, ZACHARIAH

ART UNIT PAPER NUMBER

1648

DATE MAILED: 08/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/773,530

Applicant(s)

COX, GEORGE N.

Examiner

Zachariah Lucas

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 24-46 is/are pending in the application.
- 4a) Of the above claim(s) 24 and 26-43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 25 and 44-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 2/5/04, 9/11/06.

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. Claims 24-46 are pending in the application.

Election/Restrictions

2. Applicant's election without traverse of species (b), erythropoietin (EPO) variants having a cysteine inserted at the C-terminus of the protein, in the reply filed on September 7, 2006 is acknowledged.
3. Claims 24 and 26-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 7, 2006.
4. Claims 25 and 44-46 are under consideration.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on February 4, 2004, and September 11, 2006 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 25 and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Braxton (U.S. 5,766,897- of record in the February 2004 IDS) in view of the teachings of Boissel et al. (J Biol Chem 268:15983-93 (also of record in the February 2004 IDS), Weich et al. (Exp Hematol 21: 647-55), and Lin et al. (PNAS 82: 7580-7584). These claims read on cysteine variants of the erythropoietin (EPO) protein of SEQ ID NO: 2 comprising a cysteine added to the C-terminus of the protein, wherein a polyethylene glycol (PEG) molecule has been attached to the added cysteine.

Braxton teaches the making of PEGylated variants of proteins through the substitution of addition of cysteine residues into the sequence such that the PEG molecules may be attached thereto. See e.g., abstract, columns 3 and 10. The reference teaches that the cysteine residues may be inserted into the sequence at positions of the protein that are surface exposed and are not part of the active site of the protein. See e.g., column 11 lines 22-68, and column 14 lines 52-61. The reference also identified erythropoietin as a useful protein for such modification.

Braxton does not specifically teach or suggest the addition of a C-terminal cysteine to the erythropoietin sequence for the addition of the cysteine, and therefore for attachment of the PEG.

However, the teachings in the art indicate that the C-terminal four residues of the protein are not required or involved in protein function. See e.g., Boissel, at page 15989. In addition, this reference also teaches that the N-terminus of the protein is not required for the bioactivity of the protein. Page 15987, right column. The Boissel reference teaches that additional evidence of the non-involvement of the N-terminus are the provided teaches regarding the making and activity of proteins having fusions of additional sequences to this terminus. While this reference does not

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provides similar teachings regarding the C-terminus, such teaching may be found in the Weich reference, which teaches that fusions comprising the attachment of an additional protein sequence to the C-terminus of EPO resulted in an EPO fusion comprising EPO bioactivity. Weich, page 650 right column, and pages 651 and 653. The cumulative teachings of these references therefore indicate that the C-terminus of the EPO protein is not required for the protein's activity, and that the protein remains active even when additional sequences (and therefore molecules) are attached thereto. Thus, those of ordinary skill in the art would have been motivated to use this terminus for, and had a reasonable expectation of success in, the attachment of a PEGylated cysteine.

It is additionally noted that none of these references specifically teaches that the EPO protein has the sequence of SEQ ID NO: 2. However, it is noted that the sequence of EPO, and particularly human EPO, had been previously disclosed in the art. See e.g., Lin, page 7583. The mature form of the protein disclosed by Lin is the protein of SEQ ID NO: 2. Thus, it would have been obvious to those of ordinary skill in the art to use this sequence in the making of the cysteine variant of EPO for the attachment of PEG.

The combined teachings of these references therefore render the claimed methods obvious.

Conclusion

8. No claims are allowed.
9. The following prior art reference is made of record and considered pertinent to applicant's disclosure.

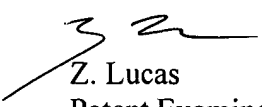
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Nielsen et al., J Immunol Methods 111: 1-9. This reference is considered relevant because, contrary to the teachings of Weich (supra), this reference teaches that an EPO fusion having a different protein fused to the C-terminus was not bioactive. However, this reference also indicates that this could be due to the prior denaturation of the protein during the isolation process. While the reference also indicates that the fusion of EPO to a large protein such as β -galactosidase could have resulted in the inactivity of the protein, this suggestion is not considered as a teaching away from the claimed invention in view of the later teachings of Weich.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Z. Lucas
Patent Examiner